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(54) 1-(3-Halo-2-pyridinyl)piperazines, processes for their preparation and pharmaceutical composition containing them.

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Description

Background of the Invention

This invention is concerned with novel 1-(3-halo-2-pyridinyl)piperazines or pharmaceutically acceptable salts thereof which have antidepressant activity and the ability to counteract the sedative side effect of antihypertensive agents. It also relates to a process for preparing the novel compounds and pharmaceutical compositions comprising the novel compounds.

The piperazinyl group is particularly ubiquitous among compounds with useful pharmacological properties. Piperazinylpyrazines (U.S. Patents 4,081,542 and 4,082,844), piperazinylquinoxalines (French patent publication 2,236,499) and 2-piperazinyl-5 (and/or 6)-substituted pyridines (U.S. Patent 4,078,063) are known anorexigenic agents which are also said to have antidepressant activity by virtue of their pharmacological influence on serotonin levels.

Now, with the present invention there is provided 1-(3-halo-2-pyridinyl)piperazines which are antidepressant agents and have the ability to counteract the sedative effect of antihypertensive agents by virtue of their ability to selectively antagonize α_2-adrenergic receptor sites.

The concept that the complex clinical state of depression is linked to a functional deficiency of monoamines in the central nervous system is now widely accepted. Numerous biochemical and clinical observations support the proposal that many forms of depressive illness are associated with reductions in adrenergic activity at functionally important sites in the brain. Thus, classical antidepressive drugs, such as amitriptyline and imipramine, are believed to act by blocking the neuronal reuptake of norepinephrine and/or serotonin, thereby enhancing the availability of the monoamines as neurotransmitters.

Combinations of norepinephrine reuptake blockers with selective α_2-adrenergic receptor antagonists, their effects being at least additive, form another aspect of this invention.

In addition to α_1-adrenergic receptors which mediate postsynaptic responses to the neurotransmitter, norepinephrine, other adrenergic receptors are present at or near sympathetic terminals. These latter receptors, α_2-adrenergic receptors, form part of a negative feedback system which modulates noradrenergic neurotransmission by controlling the impulse-induced release of norepinephrine from presynaptic terminals. Activation of α_2-adrenergic receptors results in a decrease in the amount of norepinephrine normally released from the nerve terminals by nerve impulses while antagonism of α_2-adrenergic receptors increases norepinephrine release. Therefore, molecules that block α_2-adrenergic receptors afford an alternate approach to enhancement of noradrenergic function and the treatment of depression associated with an absolute or relative deficiency of adrenergic function.

Mianserin, a clinically effective antidepressant which has been reported to have minimal *in vivo* norepinephrine reuptake inhibiting properties, blocks α_2-adrenergic receptors. However, mianserin fails to exhibit any important selectivity for α_1- or α_2-adrenergic receptors suggesting that mianserin, *in vivo*, blocks α_1-receptors at about the same dose required to block α_2-receptors [Clineschmidt et al., *Arch. Int. Pharmacodyn. Ther., 242,* 59 (1979)].

The compounds of the present invention, being highly selective for the α_2-adrenergic receptor, have definite therapeutic advantages over the more non-selective α_1-, α_2-antagonists. Since α_1- (or post-synaptic) blockade opposes the increase in nor-adrenergic transmission initiated through α_2-blockade, compounds that selectively antagonize α_2-adrenergic receptors induce enhanced neurotransmission at nor-adrenergic synapses. In addition, molecules with reduced α_1-receptor blocking properties, such as the compounds of the present invention, produce less orthostatic hypotension, an undesirable side-effect [Synder, *Pharmakopsychiat, 13,* 62 (1980)].

The limiting side effect of sedation produced by some antihypertensive agents is believed to be associated with stimulation of presynaptic α_2-/adrenergic receptors. However, the lowering of blood pressure by these antihypertensive agents is not related to these receptors, but rather to postsynaptic adrenergic receptors [Birch et al., *Br. J. Pharmacol., 68,* 107P (1979)]. Selective α_2-receptor antagonists should be useful in reducing the adverse effect of sedation produced by some antihypertensive drugs. Thus, the selective α_2-receptor blocker, yohimbine, antagonizes the sedation produced by clonidine [Drew et at., *Br. J. Pharmacol., 67* 133 (1979)] and the locomotor depressant effects of methyldopa in rats [Clineschmidt et al., *Arch. Int. Pharmacodyn. Ther., 244, 231 (1980)].* In addition, yohimbine has been reported to reduce clonidine-induced sedation in man [Autret et al., *Eur. J. Clin. Pharmacol., 12,* 319 (1977)].

The compounds of the present invention, being highly selective for the α_2-adrenergic receptor, effectively reduce the sedative effects of antihypertensive agents without affecting the blood pressure lowering properties.

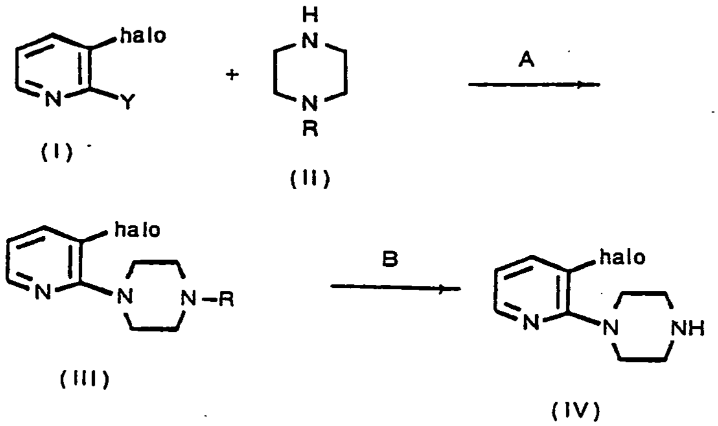
Detailed Description of the Invention

This invention is concerned with 1-(3-halo-2-pyridinyl)piperazine or a pharmaceutically acceptable salt thereof, wherein halo is chloro, bromo or fluoro, especially fluoro.

The pharmaceutically acceptable salts coming within the purview of this invention include the pharmaceutically acceptable acid-addition salts. Acids useful for preparing these acid-addition salts include, inter alia, inorganic acids, such as the hydrohalic acids (e.g., hydrochloric and hydrobromic acid), sulfuric acid, nitric acid, and phosphoric acid, and organic acids such as maleic, fumaric tartaric, citric, acetic, benzoic, 2-acetoxybenzoic, salicyclic, succinic acid, theophylline, 8-chlorotheophylline, p-aminobenzoic, p-acetamidobenzoic, methanesulfonic, or ethane disulfonic.

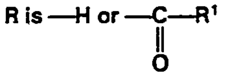
The novel compounds of the present invention are prepared by reaction of 2-Y-3-halo-pyridines of formula I with a piperazine of formula II.

The reaction sequence is as follows:



wherein

Y is halogen, especially chloro, C_{1-6}alkylsulfonyloxy, such as methanesulfonyloxy; or benzenoid arylsulfonyloxy such as benzenesulfonyloxy or toluenesulfonyloxy; or C_{1-5} alkylsulfonyl, such as methanesulfonyl; or benzenoid arylsulfonyl such as benzenesulfonyl or toluenesulfonyl and



$$R \text{ is } —H \text{ or } —\underset{\underset{O}{\|}}{C}—R^1$$

wherein R^1 is hydrogen, C_{1-3} alkyl, benzenoid aryl such as phenyl, tolyl or xylyl, C_{1-3} alkoxy, benzenoid aryloxy such as phenoxy, tolyloxy or xylyloxy, or $—NR^2R^3$ wherein R^2 and R^3 are independently hydrogen, or C_{1-3} alkyl, or R^2 and R^3 taken together are tetramethylene, pentamethylene or $—(CH_2)_2O(CH_2)_2—$.

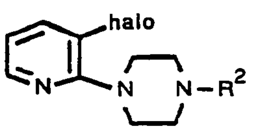
Process A takes place at temperatures ranging from about ambient to about 200°C, preferably under an inert atmosphere, e.g. N_2, He or Ar, until a substantial amount of desired compound of formula III is obtained, typically for a period of from about 0.25 to about 5 days, preferably from about 0.5 to about 3 days.

The reaction may be conducted neat, in the absence of solvent or in an inert organic solvent such as a C_{2-5} alkanol, preferably butanol, acetonitrile, dimethylformamide, or dimethylsulfoxide.

For Process B, either acidic or basic hydrolysis conditions may be used. For basic hydrolysis, an alkali metal hydroxide such as KOH or NaOH is preferred. At least 2 molar equivalents of base are necessary for best yields, but an excess of 2—10 equivalents is preferred. Solvents may be H_2O or co-solvents miscible with H_2O such as methanol ethanol, ethyleneglycol, or DMF, may be added. The hydrolysis takes place at temperatures ranging from about ambient to about 200°C, preferably under an inert atmosphere, e.g., N_2, He or Ar, typically from about 1 hour to about 2 days preferable from 3 hours to 1 day.

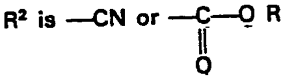
For acidic hydrolysis, dilute or concentrated aqueous mineral acids, such as HCl or HBr, or dilute or concentrated sulfuric acid is preferred. Miscible organic solvents such as ethanol, acetic acid or ethylene glycol may be added. Reaction temperatures range from ambient to about 150°C and an inert atmosphere is preferred. Reaction times from 1 hour to 2 days are required and preferred are times of 3 hours to 1 day.

Another process comprises removal of an N-alkyl, alkenyl or aralkyl group from the piperazine nitrogen. These groups are removed by reaction with one equivalent of cyanogen bromide, a carboalkoxy halide, carbohaloalkoxy halide, carboalkenoxy halide, carboaryloxyhalide or a carboaryl alkoxy halide in a non-aqueous, aprotic solvent such as ether, chloroform, toluene or benzene at a temperature from about 0°C to the reflux temperature of the solvent to give the compounds of structure V:



(V)

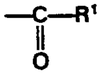
wherein



R^2 is $—CN$ or $—\underset{\underset{O}{\|}}{C}—O\ R^3$

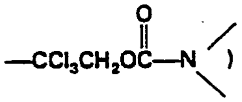
wherein R^3 is C_{1-3} alkyl, halo-C_{1-3} alkyl, C_{2-4} alkenyl, such as vinyl or 1-propenyl, benzenoid aryl such as phenyl, or benzenoid aryl-C_{1-3} alkyl such as phenyl-C_{1-3} alkyl.

These groups, R^2, are then removed by acid or base hydrolysis as previously described for hydrolysis fo the group



$—\underset{\underset{O}{\|}}{C}—R^1$

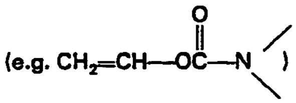
Some of the carbamates, V, are converted to the secondary amine by other routes. For example, the β,β,β-triochloroethyl carbamate



$—CCl_3CH_2O\overset{\overset{O}{\|}}{C}—N\langle\ )$

is converted to the secondary amine by heating with excess zinc dust in a C_{1-3} alkanol or aqueous acetic acid.

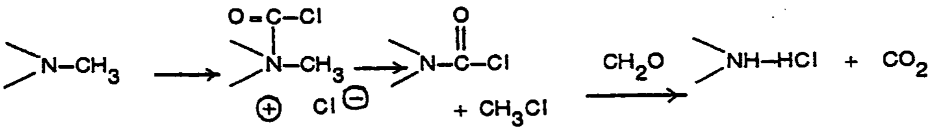
An alkenyl carbamate



(e.g. $CH_2{=}CH—O\overset{\overset{O}{\|}}{C}—N\langle\ )$

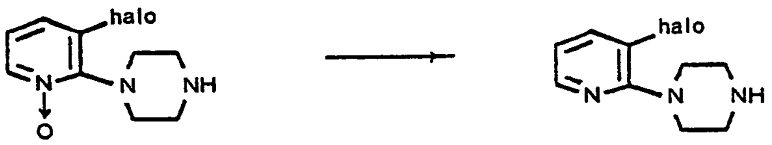
is removed by treating with anhydrous HCl in a C_{1-3} alkanol or HBr in acetic acid or $Hg(OAc)_2$ in aqueous acetic acid.

A preferred dealkylation procedure is to react a tertiary amine with phosgene, $COCl_2$, in a non-aqueous, aprotic solvent such as ether, $CHCl_3$ or toluene at about 0° to about 50°C for 1—3 days followed by the addition of excess water with vigorous stirring at about 25°C to about 100°C for 1—12 hours.



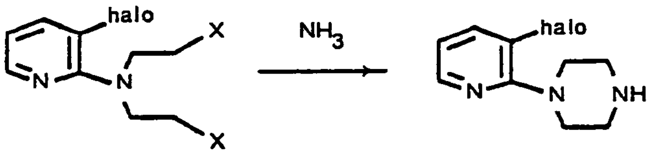
In the case of N-benzyl derivatives, the aralkyl group can be removed by all of the above procedures as well as by hydrogenation using Pd, Pt, PtO_2, or Raney Ni catalysts at about 1 atmosphere to about 50 atmospheres of pressure, at about 25—100°C for 3 hours to 1 day in a solvent such as an alcohol, acetic acid, or H_2O.

A further process is depicted as follows and comprises reduction of a pyridine-N-oxide:



Suitable reducing agents are tin, zinc, iron, or sulfur dioxide in inorganic or organic acids; triphenylphosphine, sodium arsenite, ammonium sulfide, sodium dithionite, ferrous oxalate-granulated lead; and catalytic hydrogenation over palladium on carbon, or Raney nickel. Suitable solvents include polar solvents such as water, acetic acid or lower alcohols. The reduction is conducted at from about 0° to about 150°C.

An additional process comprises formation of the piperazine ring as follows:



wherein the X groups are the same or different and X is a displaceable group such as halogen, tosyloxy mesyloxy, or trialkylammonium. In general, the above process is effected by heating the reactants at from about 0° to about 250°C in a polar solvent such as water, dimethylformamide or alcohols.

In the selective antagonizing α_2-adrenergic receptors in a patient, a novel compound or pharmaceutically acceptable salt thereof, can be administered in an amount ranging from about 0.01 to about 20 mg per kg of body weight per day, preferably from about 0.1 to about 10 mg per kg of body weight per day in a single dose or in 2 to 4 divided doses.

These doses are useful for treating depression or for treating sedation caused by antihypertensive chemotherapy.

If used in combination with a norepinephrine reuptake blocker anti-depressant, the dose of each is about half the recommended dose.

The compounds, or pharmaceutically acceptable salts thereof, of the present invention, in the described dosages, are administered orally, intraperitoneally, subcutaneously, intramuscularly, or intravenously. They are preferably administered orally, for example in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, or chewing gum, prepared by art recognized procedures. The amount of active compound in such therapeutically useful compositions or preparations is such that a suitable dosage will be obtained.

The following examples illustrate the present invention without, however, limiting the same thereto.

Example 1

1-(3-Fluoro-2-pyridinyl)piperazine dihydrochloride

A solution of 2-chloro-3-fluoropyridine (500 mg, 425 mmol) and anhydrous piperazine (3.66 g, 42.5 mmol) in 40 ml of n-butanol is stirred at reflux for 18 hours. After concentrating to dryness *in vacuo*, the residue is partitioned between toluene and dilute sodium hydroxide solution (5% w/v). The toluene layer is washed with a saturated sodium chloride solution, dried over Na_2SO_4, filtered and concentrated to 0.65 g of oil. Upon treatment of the oil with ethanolic hydrogen chloride and crystallization by dissolving the crude material in a minimum of methanol:ethanol (1:1) mixture and addition of ethyl acetate to incipient cloudiness, there is obtained 0.38 g., (35% yield) of product. m.p. 203—210°C.

Calculated for $C_9H_{12}FN_3 \cdot 2HCl$:
C, 42.53; H, 5.55; N, 16.53.
Found: C, 42.16; H, 5.64; N, 16.39.

Following the procedure substantially as described in Example 1, but substituting for the 2-chloro-3-fluoropyridine used therein, an equimolecular amount of 3-bromo-2-chloropyridine or 2,3-dichloropyridine there is produced respectively: 1-(3-bromo-2-pyridinyl)piperazine hydrochloride hemihydrate, m.p. 180°C (dec.); and 1-(3-chloro-2-pyridinyl)piperazine hydrochloride m.p. 142—144°C.

Example 2

1-(3-Fluoro-2-pyridinyl)piperazine dihydrochloride

Step A:
Preparation of 1-(3-fluoro-2-pyridinyl)-4-carbethoxy piperazine

A solution of 2-chloro-3-fluoropyridine (650 mg, 5.06 mmol) and ethyl N-piperazinocarboxylate (1.61 g, 10.2 mmol) in 60 ml of n-butanol is stirred at reflux under nitrogen for 18 hours. After concentrating to dryness under reduced pressure, the residue is dissolved in a mixture of ethyl acetate and water. The ethyl acetate extract is washed again with water, dried over anhydrous sodium sulfate, filtered and concentrated. The N-carbethoxy derivative of 1-(3-fluoro-2-pyridinyl)piperazine is further purified by chromatogrphy over silica gel 60 (230—400 mesh).

Step B:
Preparation of 1-(3-fluoro-2-pyridinyl)-piperazine dihydrochloride

A solution of 1-(3-fluoro-2-pyridinyl)-4-carbethoxy piperazine (700 mg, 2.76 mmol) in 50 ml of 6N hydrochloric acid is stirred at reflux under N_2 for 6 hours and then concentrated under reduced pressure. The residue is recrystallized from an ethanol-ethyl acetate mixture to give 1-(3-fluoro-2-pyridinyl) piperazine dihydrochloride.

Example 3
1-(3-Fluoro-2-pyridinyl)piperazine hydrogen maleate

Step A
Preparation of 1-(3-fluoro-2-pyridinyl)-4-formylpiperazine

A solution of 2-chloro-3-fluoropyridine (500 mg, 4.25 mmol) and 1-piperazinecarboxaldehyde (970 mg, 850 mmol) in 40 ml of n-butanol is stirred at reflux for 18 hours under nitrogen. After concentrating to dryness *in vacuo*, the residue is partitioned between toluene and water. The toluene extract is washed with a saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated to an oil. The N-formyl derivative is purified by chromatography over silica gel 60 (230—400 mesh).

Step B:
Preparation of 1-(3-fluoro-2-pyridinyl)piperazine hydrogen maleate

A solution of 1-(3-fluoro-2-pyridinyl)-4-formylpiperazine (400 mg, 1.91 mmol) in 50 ml of ethanol containing 12 ml of 10% sodium hydroxide solution is stirred at reflux for 10 hours under nitrogen. After removing most of the ethanol under reduced pressure at 40—45°C, organic products are extracted into toluene. The toluene extract is washed with a saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated to an oil. This oil is dissolved in ethanol, treated with an equivalent of maleic acid, and the hydrogen maleate salt of 1-(3-fluoro-2-pyridinyl) piperazine is precipitated by the addition of ethyl acetate.

1-(3-Fluoro-2-pyridinyl)piperazine hydrogen maleate has m.p. 165—166°C.

Example 4
1-(3-Fluoro-2-pyridinyl)piperazine hydrogen maleate

Step A:
Preparation of 1-methyl-4-(3-fluoro-2-pyridinyl)piperazine

A solution of 2-chloro-3-fluoropyridine (1.0 g, 8.5 mmol) and N-methyl piperazine (4.26 g, 42.5 mmol) in n-butano, 50 ml, is stirred at reflux for 18 hours. After concentrating under reduced pressure at 50°C, the residue is partitioned between ethyl ether and 5% NaOH solution. The ethyl ether extract is washed with a saturated sodium chloride solution dried over Na_2SO_4, filtered and concentrated under reduced pressure. The oily product is converted to the hydrogen fumarate salt, m.p. 148—149°C, by treatment with fumaric acid in methanol and precipitation with ethyl ether.

Step B:
Preparation of 1-(3-fluoro-2-pyridinyl)piperazine hydrogen maleate

To a solution of 1-methyl-4-(3-fluoro-2-pyridinyl)piperazine (0.98 g, 5.0 mmol) in toluene, 25 ml, cooled with an ice bath is added 3.96 g. of a 12.5% solution of phosgene in toluene. After stirring at 5—10°C for 1 hour, the mixture is allowed to warm to 20—25°C and remain at this temperature for 3 days. Water, 10 ml, is then added and the mixture stirred vigorously at 50°C for 6 hours. The water layer is removed, made basic with 10% NaOH solution and the product extracted with ethyl acetate. The ethyl acetate extract is washed with a saturated NaCl—H_2O solution, dried over anhydrous sodium sulfate, filtered and concentrated to an oil. This oil is dissolved in ethanol, treated with an equivalent of maleic acid, and the hydrogen maleate salt precipitated by the addition of ethyl acetate.

Example 5
1-(3-Fluoro-2-pyridinyl)piperazine dihydrochloride

Step A:
Preparation of 1-benzyl-4-(3-fluoro-2-pyridinyl)piperazine dihydrochloride

A solution of 2-chloro-3-fluoropyridine (1.0 g, 8.5 mmol) and N-benzylpiperazine (3.0 g, 17 mmol) in n-butanol, 50 ml, is stirred at reflux for 24 hours. After concentrating under reduced pressure at 50°C, the residue is partitioned between ethyl acetate and a 5% sodium hydroxide solution. The toluene layer is washed with a saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated to an oil. Upon treatment of the oil with ethanolic hydrogen chloride and recrystallization from an ethanol-ethyl acetate mixture there is obtained the dihydrochloride of 1-benzyl-4-(3-fluoro-2-pyridinyl)piperazine.

Step B:
Preparation of 1-(3-fluoro-2-pyridinyl)piperazine dihydrochloride

A solution of 1-benzyl-4-(3-fluoro-2-pyridinyl)piperazine dihydrochloride (500 mg, 1.8 mmol) in glacial acetic acid, 20 ml, is shaken with 100 mg of a platinum oxide catalyst in an atmosphere of hydrogen at 50°C and 2 atmospheres pressure until one equivalent of hydrogen has been taken up. The catalyst is removed by filtration and the filtrate concentrated under reduced pressure. The residue is recrystallized from an ethanol-ethyl acetate mixture to give the dihydrochloride of 1-(3-fluoro-2-pyridinyl)piperazine.

Example 6
1-(3-Fluoro-2-pyridinyl)piperazine dihydrochloride

Step A:
Preparation of 2-chloro-3-fluoropyridine N-oxide

A mixture of 2-chloro-3-fluoropyridine (11.8 g, 0.10 mol) and 11.4 ml of 30% hydrogen peroxide in acetic acid, 70 ml, is stirred at 75°C for 4 hours. Additional 30% hydrogen peroxide, three 5 ml portions, is added over 24 hours followed by 3 ml of a saturated sodium bisulfite solution. The reaction mixture is concentrated to approximately 25 ml under reduced pressure at 55—60°C, diluted with water, 30 ml, and made basic with potassium carbonate. The crude N-oxide is extracted into ethyl acetate, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Chromatography over silica gel and elution with 2% MeOH — 98% $CHCl_3$ (v/v) mixture gives 2-chloro-3-fluoropyridine N-oxide as a liquid.

Step B:
Preparation of 2-(1-piperazinyl)-3-fluoropyridine N-oxide

A solution of 2-chloro-3-fluoropyridine N-oxide (400 mg, 3.0 mmol) and piperazine (1.3 g, 15 mmol) in n-butanol, 15 ml, is stirred at reflux for 20 hours. After concentrating under reduced pressure at 55—60°C, the residue is chromatographed over silica gel and the crude N-oxide eluted with a 50% methanol-methylene chloride solvent mixture. The appropriate eluate is concentrated to an oily residue of the title compound.

Step C:
Preparation of 1-(3-fluoro-2-pyridinyl)piperazine dihydrochloride

A solution of 3-fluoro-2-piperazinylpyridine N-oxide (2 mmol) in 10 ml of glacial acetic acid is warmed to about 85°C saturated with anhydrous hydrogen chloride gas and treated with a fine stream of sulfur dioxide for 1 hour. The acetic acid is removed under reduced pressure and the residue is crystallized from an ethanol-ethyl acetate mixture to give the title compound.

Example 7
1-(3-Fluoro-2-pyridinyl)piperazine hydrogen maleate

Step A:
Preparation of 2-[N,N-bis(2-hydroxyethyl)amino]-3-fluoropyridine

A solution of 2-chloro-3-fluoropyridine (1.0 g, 8.5 mmol) and diethanolamine (2.1 g, 20 mmol) in n-butanol, 50 ml, is stirred at reflux under nitrogen for 20 hours. After removing most of the n-butanol under reduced pressure at about 50°C, the residue is partitioned between ethyl acetate and 5% sodium hydroxide solution. The ethyl acetate layer is washed with a saturated solution of sodium chloride in water, dried over anhydrous sodium sulfate, filtered and concentrated. Chromatography of the residue over silica gel 60 (230—400 mesh) gives 2-[N,N-bis(2-hydroxyethyl)amino]-3-fluoropyridine.

Step B:
Preparation of 2-[N-N-bis(2-chloroethyl)amino]-3-fluoropyridine hydrochloride

The diol product from Step A (800 mg, 4.0 mmol) is added to thionyl chloride, 10 ml, cooled to about 5°C with an ice bath. The solution is allowed to warm to about 20°C and then stirred at reflux for 6 hours. Unreacted thionyl chloride is removed under reduced pressure at about 45°C. Toluene, 10 ml, is added and then concentrated under reduced pressure at about 50°C. This process is repeated two more times to ensure complete removal of unreacted thionyl chloride from the residual dichloride hydrochloride.

Step C:
Preparation of 1-(3-fluoro-2-pyridinyl)piperazine hydrogen maleate

The crude dichloride hydrochloride residue from Step B is dissolved in absolute ethanol, 50 ml, saturated with anhydrous ammonia at about 20°C and heated in a sealed vessel at about 100°C for 20 hours. After concentrating under reduced pressure at about 40—45°C, product is extracted into toluene. The toluene extract is washed with a saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated to an oil. This oil is purified by chromatography over silica gel 60 (230—400 mesh) with elution by a 5% methanol-95% chloroform saturated with ammonia mixture and converted to the hydrogen maleate salt with an equivalent of maleic acid in ethanol-ethyl acetate.

Example 8

Adrenergic Receptor Binding Assays for 1-(3-Halo-2-pyridinyl)piperazines and Related Compounds

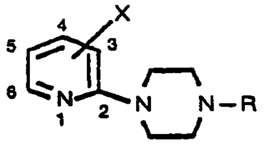
The α_1 and α_2-adrenergic receptor binding was determined for 1-(3-halo-2-pyridinyl)piperazines and a number of other structurally related compounds shown in Table I.

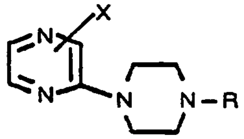
Extent of binding to the α_1-adrenergic receptor was determined by the method of Greengrass and Bremner, *Eur. J. Pharmacol.*, *55*, 323 (1979) and is expressed in Table I as Ki, representing the affinity of each compound for the [^{3}H] prazosin binding site in calf cerebral cortex.

Binding to the α_2-adrenergic receptor was determined by the method of Lyon and Randall, *Life Sciences*, *26*, 1121 (1980) and also is expressed in Table I as Ki representing the affinity of each compound for the [^{3}H] clonidine binding site in calf cerebral cortex.

TABLE I

Adrenergic Receptor Binding of 1-(3-Halo-2-pyridinyl)piperazine and Related Compounds



Compound	X	R	Adrenergic Binding Ki(nM)		
			α_2	α_1	Ratio α_1/α_2
1	3-F	H	7.6	5000	658
2	3-Cl	H	7.8	2000	256
3	3-Br	H	11	1700	155
4	3-I	H	26	1500	58
5[a]	3-Br	$-CH_3$	3.1	200	65
6[b]	6-Cl	H	18	500	26
7[c]	H	H	35	2900	83
8[b]	5-Cl	H	1000	—	—
					
9[d]	6-Cl	H	127	2400	19
10	3-Cl	H	160	26000	163

a) Ann. Pharm. franc. *32*, 569 (1974).
b) U.S. Patent 4,078,063.
c) U.S. Patent 3,773,951.
d) U.S. Patent 4,082,844.

Of the compounds tested, the novel compounds of this invention (1, 2 and 3) clearly have the strongest affinity (lowest Ki), with the exception of compound 5, for the α_2-adrenergic receptors, and the weakest affinity (highest Ki) for the α_1-adrenergic receptors. Accordingly they have the greatest selectivity or ratio of $Ki_{\alpha 1}/Ki_{\alpha 2}$ as compared to any of the other tested compounds.

Example 9

Pharmaceutical Formulation

Ingredient	mg/Capsule
1-(3-fluoro-2-pyridinyl) piperazine dihydrochloride	6
starch	87
magnesium stearate	7

The active ingredient, starch and magnesium stearate are blended together. The mixture is used to fill hard shell capsules of a suitable size at a fill weight of 100 mg per capsule.

Example 10

Pharmaceutical Formulation — including a norepinephrine reuptake blocker

Ingredients	mg/capsule
1-(3-fluoro-2-pyridinyl)piperazine dihydrochloride	3
amitriptyline hydrochloride	15
starch	75
magnesium stearate	7

The active ingredients, starch and magnesium stearate are blended together. The mixture is used to fill hard shell capsules of a suitable size at a fill weight of 100 mg per capsule.

Example 11

Pharmaceutical Formulation including an antihypertensive agent

Ingredients	mg/capsule
1-(3-fluoro-2-pyridyl)piperazine dihydrochloride	6
methyldopa	250
starch	219
magnesium stearate	25

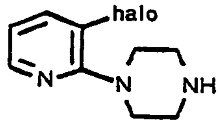
The active ingredient, starch and magnesium stearate are blended together. The mixture is used to fill hard shell capsules of a suitable size at a fill weight of 500 mg per capsule.

Claims

1. A process for the preparation of 1-(3-halo-2-pyridinyl)piperazine, wherein halo is chloro, bromo or fluoro which comprises the treatment of a 2-Y-3-halopyridine with piperazine, wherein Y is halogen, C_{1-5} alkylsulfonyloxy, benzenesulfonyloxy or toluenesulfonyloxy.

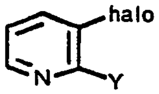
2. The process of Claim 1 wherein halo is fluoro and Y is chloro.

3. A process for the preparation of 1-(3-halo-2-pyridinyl)piperazine, of structural formula IV:



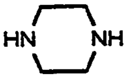
(IV)

wherein halo is chloro, bromo or fluoro which comprises:
a) treatment of a 3-halo pyridine of structural formula I:



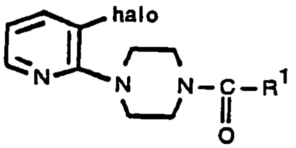
(I)

wherein Y is fluoro, chloro, bromo, iodo, C_{1-5} alkylsulfonyloxy, or benzenoid arylsulfonyloxy, C_{1-5} alkylsulfonyl, or benzenoid arylsulfonyl, with a compound of structural formula II:

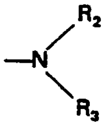


; (II)

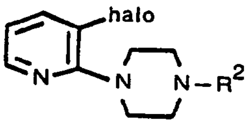
b) treatment of a compound of structural formula



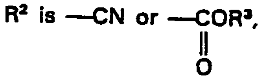
with an acid or a base, wherein R^1 is hydrogen, C_{1-3} alkyl, benzenoid aryl, C_{1-5} alkoxy, benzenoid aryloxy or



wherein
R^2 and R^3 are independently hydrogen or C_{1-3} alkyl, or R^2 and R^3 taken together are tetramethylene, pentamethylene or $(CH_2)_2O(CH_2)_2$—;
c) treatment of a compound of structural formula



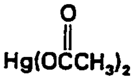
with an acid or a base, wherein



R^2 is $—CN$ or $—\underset{\underset{O}{\|}}{C}OR^3$,

wherein R^3 is halo-C_{1-3} alkyl, C_{2-4} alkenyl, or benzenoid aryl C_{1-3} alkyl;
d) treatment of the compound wherein R^3 is CCl_3CH_2— with heat and zinc dust in a C_{1-3} alkanol or aqueous acetic acid;

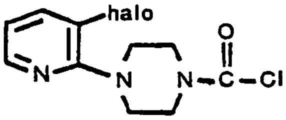
e) treatment of the compound wherein R^3 is C_{2-4} alkenyl with an anhydrous hydrogen halide in a C_{1-3} alkanol or acetic acid or with



$$Hg(O\overset{\overset{O}{\|}}{C}CH_3)_2$$

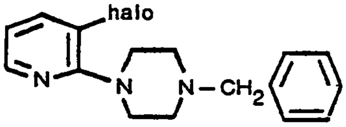
in aqueous acetic acid;

f) treatment of a compound of structural formula:



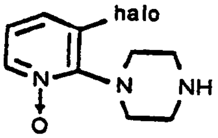
with water;

g) treatment of a compound of structural formula:



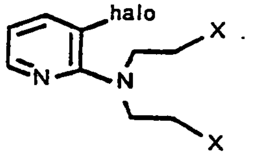
with hydrogen in the presence of a hydrogenation catalyst;

h) treatment of a compound of structural formula:



with a reducing agent;

i) treatment of a compound of structural formula:



with ammonia wherein the X groups are the same or different and X is halo, tosyloxy, mesyloxy, or trialkylammonium.

4. The process of Claim 3, wherein halo is fluoro.

5. The compound 1-(3-halo-2-pyridinyl)piperazine or a pharmaceutically acceptable salt thereof, wherein halo is chloro, bromo or fluoro.

6. The compound of Claim 5 which is 1-(3-fluoro-2-pyridinyl)piperazine or a pharmaceutically acceptable salt thereof.

7. An antidepressant pharmaceutical formulation comprising a pharmaceutical carrier and an effective antidepressant amount of 1-(3-halo-2-pyridinyl)piperazine or a pharmaceutically acceptable salt thereof, wherein halo is chloro, bromo or fluoro.

8. The formulation of Claim 7 wherein the compound is 1-(3-fluoro-2-pyridinyl)piperazine or a pharmaceutically acceptable salt thereof.

9. An antidepressant pharmaceutical formulation comprising a pharmaceutical carrier, an effective amount of an antidepressant which acts by norepinephrine reuptake blockade and an effective antidepressant amount of the compound 1-(3-halo-2-pyridinyl)piperazine or a pharmaceutically acceptable salt thereof, wherein halo is chloro, bromo, or fluoro.

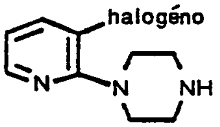
10. The antidepressant formulation of Claim 9 wherein the compound is 1-(3-fluoro-2-pyridinyl)-piperazine or a pharmaceutically acceptable salt thereof.

Revendications

1. Procédé de préparation d'une 1-(3-halogéno-2-pyridinyl)pipérazine dans laquelle halogéno est chloro, bromo ou fluoro, qui comprend le traitement d'une 2-Y-3-halogénopyridine avec la pipérazine, dans laquelle Y représente un atome d'halogène, un groupe alkylsulfonyloxy en C_{1-5}, benzènesulfonyloxy ou toluènesulfonyloxy.

2. Procédé selon la revendication 1, dans lequel halogéno est fluoro et Y est chloro.

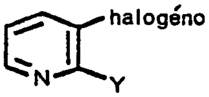
3. Procédé de préparation d'une 1-(3-halogéno-2-pyridinyl)pipérazine de formule structurale IV:



(IV)

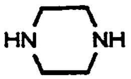
dans laquelle halogéno est chloro, bromo ou fluoro, qui consiste:

a) à traiter une 3-halogéno-pyridine de formule structurale I:



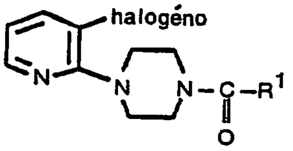
(I)

dans laquelle Y est fluoro, chloro, bromo, iodo, alkylsulfonyloxy en C_{1-5} ou benzénoide-arylsulfonyloxy, alkylsulfonyle en C_{1-5} ou benzénoide-arylsulfonyle avec un composé de formule structurale II:

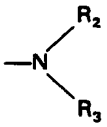


(II)

b) à traiter un composé de formule structurale



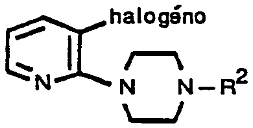
avec un acide ou une base, dans laquelle R^1 est un atome d'hydrogène, un radical alkyle en C_{1-3}, benzénoïde-aryle alcoxy en C_{1-5} benzénoïde-aryloxy ou



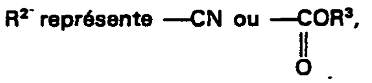
$$-N\begin{matrix}R_2\\R_3\end{matrix}$$

dans lequel R^2 et R^3 représentent indépendamment un atome d'hydrogène ou un radical alkyle en C_{1-3}, ou bien R^2 et R^3 représentent conjointement le tétraméthylène, le pentaméthylène ou le groupe $-(CH_2)_2O(CH_2)_2-$;

c) à traiter un composé de formule structurale



avec un acide ou une base, dans laquelle

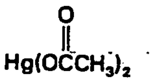


$$R^2 \text{ représente } -CN \text{ ou } -\underset{\underset{O}{\|}}{C}OR^3,$$

dans lequel R^3 est un radical halogénoalkyle en C_{1-3}, alcényle en C_{2-4} ou benzénoïde-arylalkyle en C_{1-3};

d) à traiter le composé dans lequel R^3 représente CCl_3CH_2 par la chaleur et la poussière de zinc dans un alcanol en C_{1-3} ou l'acide acétique aqueux;

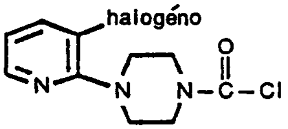
e) à traiter le composé dans lequel R^3 est un radical alcényle en C_{2-4} avec un acide halogénhydrique anhydre dans de l'alcanol en C_{1-3} ou l'acide acétique ou avec



$$Hg(O\overset{\overset{O}{\|}}{C}CH_3)_2$$

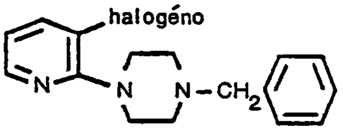
dans l'acide acétique aqueux;

f) à traiter un composé de formule structurale



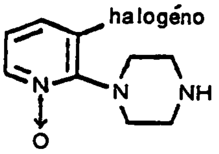
avec de l'eau;

g) à traiter un composé de formule structurale



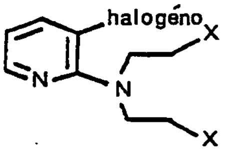
avec de l'hydrogène en présence d'un catalyseur d'hydrogénation;

h) à traiter un composé de formule structurale



avec un agent réducteur;

i) à traiter un composé de formule structurale:



avec de l'ammoniac, dans laquelle les groupes X sont identiques ou différents et X représente halogéno, tosyloxy, mésyloxy, ou trialkylammonium.

4. Procédé selon la revendication 3, dans lequel halogéno est fluoro.

5. Le composé 1-(3-halogeno-2-pyridinyl)pipérazine ou un sel pharmaceutiquement acceptable de celle-ci, dans lequel halogéno est chloro, bromo ou fluoro.

6. Composé selon la revendication 5 qui est 1-(3-fluoro-2-pyridinyl)pipérazine ou un sel pharmaceutiquement acceptable de celle-ci.

7. Composition pharmaceutique antidépressive comprenant un véhicule pharmaceutique ou une proportion antidépressive efficace de 1-(3-halogéno-2-pyridinyl)pipérazine ou d'un sel pharmaceutiquement acceptable de celle-ci, halogéno étant chloro, bromo ou fluoro.

8. Composition selon la revendication 7, dans laquelle le composé est la 1-(3-fluoro-2-pyridinyl)pipérazine ou un sel pharmaceutiquement acceptable de celle-ci.

9. Composition pharmaceutique antidépressive comprenant un véhicule pharmaceutique, une quantité efficace d'un antidépresseur agissant par blocage de la réabsorption de la norepinephrine et une quantité antidépressive efficace du composé 1-(3-halogéno-2-pyridinyl)pipérazine ou d'un sel pharmaceutiquement acceptable de celle-ci, halogéno étant chloro, bromo ou fluoro.

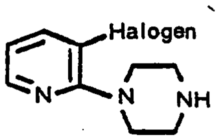
10. Composition antidépressive selon la revendication 9, dans laquelle le composé est 1-(3-fluoro-2-pyridinyl)pipérazine ou un sel pharmaceutiquement acceptable de celle-ci.

Patentansprüche

1. Verfahren zur Herstellung von 1-(3-Halogen-2-pyridinyl)piperazin, worin Halogen Chlor, Brom oder Fluor bedeutet, durch Behandeln eines 2-Y-3-Halogenpyridins mit Piperazin, worin Y Halogen-C_{1-5}-alkylsulfonyloxy, Benzolsulfonyloxy oder Toluolsulfonyloxy ist.

2. Verfahren nach Anspruch 1 worin Halogen Fluor und Y Chlor ist.

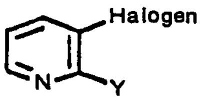
3. Verfahren zur Herstellung von 1-(3-Halogen-2-pyridinyl)piperazin mit der Strukturformel IV:



(IV)

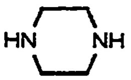
worin Halogen Chlor, Brom oder Fluor ist, durch

a) Behandeln eines 3-Halogen-pyridins der Strukturformel I:



(I)

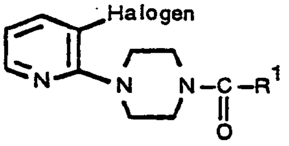
worin Y Fluor, Chlor, Brom, Jod, C_{1-5}-Alkylsulfonyloxy oder Benzenoid-arylsulfonyloxy, C_{1-5}-Alkylsulfonyl oder Benzenoid-arylsulfonyl ist, mit einer Verbindung der Strukturformel II:



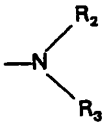
;

(II)

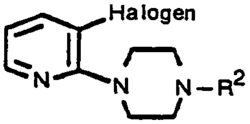
b) Behandeln einer Verbindung der Strukturformel



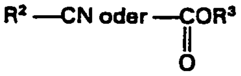
mit einer Säure oder einer Base, worin R_1 Wasserstoff C_{1-3}-Alkyl, Benzenoid-aryl, C_{1-5}-Alkoxy, Benzenoidaryloxy oder



ist, worin
R^2 und R^3 unabhängig Wasserstoff oder C_{1-3}-Alkyl sind, oder R^2 und R^3 zusammengenommen Tetramethylen, Pentamethylen oder $—(CH_2)_2O(CH_2)_2—$ sind;
c) Behandeln einer Verbindung der Strukturformel

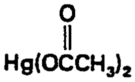


mit einer Säure oder einer Base, worin



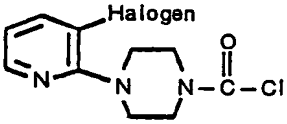
$$R^2\ —CN\ \text{oder}\ —\underset{\underset{O}{\|}}{C}OR^3$$

ist, worin R^3 Halogen-C_{1-3}-alkyl, C_{2-4}-Alkenyl oder Benzenoid-aryl-C_{1-3}-alkyl ist;
d) Behandeln der Verbindung worin R^3 CCl_3CH_2- ist, mit Wärme und Zinkstaub in einem C_{1-3}-Alkanol oder wässriger Essigsäure;
e)Behandeln der Verbindung worin R^3 C_{2-4}-Alkenyl ist mit einem wasserfreien Halogenwasserstoff in einem C_{1-3}-Alkanol oder Essigsäure opder mit

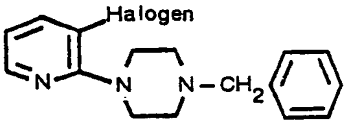


$$Hg(O\overset{\overset{O}{\|}}{C}CH_3)_2$$

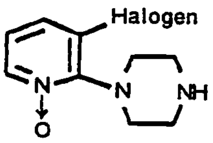
in wässriger Essigsäure;
f) Behandeln einer Verbindung der Strukturformel:



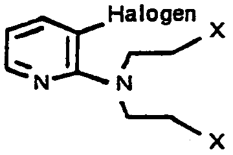
mit Wasser;
g) Behandeln einer Verbindung der Strukturformel:



mit Wasserstoff in Anwesenheit eines Hydrierungskatalysators;
h) Behandeln einer Verbindung der Strukturformel:



mit einem Reduktionsmittel;
i) Behandeln einer Verbindund er Strukturformel:



mit Ammoniak, worin die Gruppen X gleich oder verschieden sind und X Halogen, Tosyloxy, Mesyloxy oder Trialkylammonium ist.

4. Verfahren nach Anspruch 3, worin Halogen Fluor ist.

5. Die Verbindung 1-(3-Halogen-3-pyridinyl)-piperazin oder ein pharmazeutisch brauchbares Salz davon, worin Halogen Chlor, Brom oder Fluor ist.

6. Die Verbindung nach Anspruch 5, nämlich 1-(3-Fluor-2-pyridinyl)-piperazin oder ein pharmazeutisch brauchbares Salz davon.

7. Antidepressive pharmazeutische Formulierung, enthaltend einen pharmazeutischen Träger und eine antidepressiv wirksame Menge von 1-(3-Halogen-2-pyridinyl)-piperazin oder einem pharmazeutisch brauchbaren Salz davon, worin Halogen Chlor, Brom oder Fluor ist.

8. Formulierung nach Anspruch 7, worin die Verbindung 1-(3-Fluor-2-pyridinyl)-piperazin oder ein pharmazeutisch brauchbares Salz davon ist.

9. Antidepressive pharmazeutische Formulierung, enthaltend einen pharmazeutischen Träger, eine wirksame Menge eines antidepressiven Mittels, das durch eine Blockade der Norepinephrin-Resorption wirkt, und eine antidepressiv wirksame Menge der Verbindung 1-(3-Halogen-2-pyridinyl)-piperazine oder eines pharmazeutisch brauchbaren Salzes davon, worin Halogen Chlor, Brom oder Fluor ist.

10. Antidepressive Formulieruing nach Anspruch 9, worin die Verbindung 1-(3-Fluor-2-pyridinyl)-piperazine oder ein pharmazeutisch brauchbares Salz davon ist.